

**REMARKS**

Claims 1, 4, 23, 28-38, 49-51 and 53-58 are pending; claims 28-35 and 38 are currently withdrawn from consideration. Reconsideration is respectfully requested.

**Summary**

1. The pending claims all require a spray-dried solid dispersion consisting of a sparingly water-soluble drug and HPMCAS, the drug being molecularly dispersed and completely amorphous in the dispersion. In addition, the dispersion is a homogeneous solid solution of the drug in the HPMCAS.
2. There is no mention whatsoever in any of the references that a completely amorphous drug molecularly dispersed in a spray-dried solid HPMCAS/drug dispersion is made or could be made.
3. None of the references inherently disclose a completely amorphous drug molecularly dispersed in a spray-dried solid HPMCAS/drug dispersion. The Examiner asserts that the cited references disclose solvents, HPMCAS, and a drug the same as or similar to the presently claimed invention and the references mention the solutions can be spray-dried and thus the product these references form is inherently completely amorphous. This is incorrect.
  - a. To establish inherency the result must *necessarily* be so.
  - b. The Newman § 1.132 Declaration and evidence therein confirm that spray drying even the same solutions do *not* necessarily produce a completely amorphous solid dispersion - different spray-drying process conditions produce crystalline, amorphous or a mixture of crystalline and amorphous solid dispersions depending on the conditions used.
4. The cited references do not disclose any spray-drying process conditions so there is no way to practice the references' spray-drying disclosures to produce a spray-dried solid dispersion to determine the crystallinity of the references' solid dispersions. Applicant demonstrates that the cited references do not enable spray drying completely amorphous solid dispersions (Beyerinck § 1.132 Declaration).
5. Applicant's specification provides detailed guidance as to spray-drying process conditions that could be used to produce a completely amorphous drug molecularly dispersed in a spray-dried solid HPMCAS/drug dispersion.
6. Applicant demonstrates that developing spray drying processes and determining process conditions to make a completely amorphous drug molecularly dispersed in a spray-dried solid HPMCAS/drug dispersion was much more than routine experimentation.

**Discussion**

**1. The pending claims all require a spray-dried solid dispersion consisting of a sparingly water-soluble drug and HPMCAS, the drug being molecularly dispersed and completely amorphous in the dispersion. In addition, the dispersion is a homogeneous solid solution of the drug in the HPMCAS.**

The prior art, to anticipate or make obvious the present claims, must disclose the following:

- A spray dried solid homogeneous dispersion consisting of a drug and HPMCAS;
- the drug being molecularly dispersed and completely amorphous in the dispersion.

As recognized by the Examiner, none of the cited references teach or suggest a spray-dried solid dispersion with the drug being completely amorphous in the dispersion. The Examiner instead asserts that the references inherently disclose completely amorphous spray dried solid dispersions (Office Action p. 3). This is incorrect (as explained below).

**2. There is no mention whatsoever in any of the references that a completely amorphous drug molecularly dispersed in a spray-dried solid HPMCAS/drug dispersion is made or could be made.**

As recognized by the Examiner, none of the references even mention of a completely amorphous drug in a solid dispersion or a completely amorphous drug in a spray-dried solid dispersion or a spray-dried HPMCAS/drug solid dispersion wherein the drug is molecularly dispersed and completely amorphous in the dispersion.

**3. None of the references inherently disclose a completely amorphous drug molecularly dispersed in a spray-dried HPMCAS/drug solid dispersion.**

The Examiner asserts that the cited references disclose solvents, HMPCAS, and a drug and mention the solutions can be spray-dried and thus the product these references form is inherently completely amorphous spray-dried solid dispersions. This is incorrect.

- a. To establish inherency the result must necessarily be so.
- b. The Newman § 1.132 Declaration and evidence therein confirm that spray drying even the same solutions does not necessarily produce a completely amorphous solid dispersion - different spray-drying process conditions produce crystalline, amorphous or a mixture of crystalline and amorphous solid dispersions depending on the process conditions used.
- c. Because the process conditions for spray drying must be carefully determined to make a completely amorphous solid dispersion, the Examiner's assertion that the references necessarily

(i.e., inherently) disclose completely amorphous spray-dried solid solutions is improper and anticipation of the claims has not been proven.

4. **The cited references do not disclose any spray-drying process conditions so there is no way to practice the references' spray-drying disclosures to produce a spray-dried solid dispersion to determine the crystallinity of the references' solid dispersions. Applicant demonstrates that the cited references do not enable spray drying completely amorphous solid dispersions (Beyerinck § 1.132 Declaration).**
  - a. Not a single reference cited provides any direction or guidance whatsoever as to how to perform a spray drying process.
  - b. The Examiner asserts that the PTO has no laboratories so cannot practice the reference's disclosures to determine if the suggested spray-dried products would be completely amorphous (Office Action p. 12). However, because none of the references provide any disclosure as to the conditions and parameters for a spray drying process, there is no way Applicant can test such disclosures— there is no disclosure of a spray drying process to test.
  - c. As shown in the Beyerinck § 1.132 Declaration, many parameters of spray drying processes will affect whether the resulting HPMCAS/drug spray-dried molecularly dispersed and completely amorphous is produced. Besides listing such process parameters that need to be known to produce a HPMCAS/drug spray-dried molecularly dispersed and completely amorphous solid dispersion in this § 1.132 Declaration, which determination of required extensive R&D, the Declarant also evidences how little was known as to spray-drying completely amorphous solid dispersions at all, in 1997, the effective filing date of the present application. Although it is nearly impossible to prove an absence of technology (it is self-evident that proving a negative is inherently problematic if not impossible), the Declarant discusses the Chidavaenzi article that illustrates how little was known about spray drying completely amorphous solid dispersions in 1997, let alone nothing being known about spray drying HPMCAS/drug molecularly dispersed and completely amorphous solid dispersions.
5. **Applicant's specification provides detailed guidance as to spray-drying process conditions that could be used to produce a completely amorphous drug molecularly dispersed in a spray-dried solid HPMCAS/drug dispersion.**
  - a. Both § 1.132 Declarations submitted herewith indicate that those Declarants believe that the present application has sufficient direction, guidance and examples in the specification such that one of ordinary skill in the art in August of 1997 could have made a spray dried solid dispersion consisting of a sparingly water-soluble drug and HPMCAS, the drug being molecularly dispersed and amorphous in the dispersion, having a drug:polymer weight ratio between 1:0.4 and 1:20,

and the dispersion being a homogeneous solid solution of said drug in the HPMCAS with little or no experimentation, through reading Applicant's disclosure.

- b. There is particular guidance for making the claimed solid dispersions in the specification at, for example, p. 15, lines 16-19, p. 15, line 25 to p. 16, line 26, p. 21, line 23 to p. 24, line 9 and examples 15, 23, 1, 25, 26, 28 and 30.
- c. The Examiner asserts that Applicant has not provided a list of solvents and conditions suitable for making the claimed solid dispersions (Office Action p. 12). This is incorrect as evidenced by the § 1.132 Declarations, Applicant's specification (see paragraph b. above), and as shown in particular the description of solvents in the present specification at p. 17, line 3-17.

6. **Applicant demonstrates that developing spray drying processes to make a completely amorphous drug molecularly dispersed in a spray-dried solid HPMCAS/drug dispersion was much more than routine experimentation and the asserted references are not enabling for making such solid dispersions.**

Applicant presents evidence that the references fail to enable one of ordinary skill in the art to make spray dried solid dispersions of a drug and HPMCAS wherein the drug is molecularly dispersed in the dispersion (claim 1), the drug is completely amorphous in the dispersion (claim 1), the drug is homogeneous in the dispersion (claim 1), and the drug is a solid solution in HPMCAS (claim 1). Applicant also presents evidence that producing the claimed solid dispersions was much more than mere experimentation (see the Beyerinck § 1.132 Declaration and the information below).

First, Applicant notes that the Examiner asserts Applicant has not shown Miyajima, Kigoshi and Hikosaka drugs and HPMCAS could not be dissolved in a common solvent (Office Action p. 11). Applicant respectfully asserts that this is not relevant to the present issue as it is not the ability to dissolve the drugs in a common solvent that is lacking in these references but instead it is the complete failure of these references to disclose a spray dried HPMCAS/drug molecularly dispersed and completely amorphous solid dispersion or to disclose how to spray dry such a solid dispersion. The references are not enabling as to making the claimed spray-dried solid dispersions - naming of a product without enabling one of ordinary skill in the art as to how to make the product is insufficient to support rejections of the claims.

#### The Law of Enablement in Regard to Prior Art References

In order to act as anticipating prior art, a reference (or combination of references) must enable one of ordinary skill in the art to make the invention without undue experimentation. *Impax Laboratories Inc. v. Aventis Pharmaceuticals Inc.*, 545 F.3d 1312 (Fed. Cir. 2008). In other words, the prior art must inform as to how to make the claimed invention. *Minn. Mining & Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1301 (Fed. Cir. 2002).

The naming of a spray dried composition in a reference, without more, cannot constitute a description of the spray dried composition and the reference is not enabling prior art. One of ordinary skill in the art must be able to make or synthesize the composition for the reference to be considered enabling prior art for the teaching of the composition. *In re Hoeksema*, 399 F.2d 269 (CCPA 1968). In *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009) the court further confirmed the court's holding in *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988), as reinvigorated by the Supreme Court in *KSR (KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727 (2007), that the cited references must contain "detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful." (Emphasis added.)

Lack of Enablement of the Miyajima, Kigoshi and Hikosaka References for that which they are Cited

The Miyajima, Kigoshi and Hikosaka references all simply in passing mention that compositions might be spray dried, but none of the examples or enabled disclosed compositions are for making spray dried solid dispersions consisting of HPMCAS and a molecularly dispersed, completely amorphous drug in the dispersion.

- i. As discussed in the record of this application, each of these references makes only a passing mention of spray drying and nothing more. None of the references give any guidance, let alone sufficient detail, for one of ordinary skill in the art to make the spray dried solid dispersion claimed by Applicant.
- ii. The references do not provide sufficient information necessary to make the claimed spray dried dispersions, which require HPMCAS/drug-solution droplets be sufficiently dry enough by the time they reach a wall of a suitable spray drying apparatus that they are essentially solid, so that they form a fine powder and do not stick to the apparatus wall, or so that the spray dried dispersion is a homogeneous solid solution with the drug being molecularly dispersed and amorphous therein. See the Beyerinck § 1.132 Declaration of for further discussion in this regard.
- iii. As discussed in the record of this application, none of the references teach how to make or enable making of a spray dried solid dispersion where the drug is completely amorphous in the dispersion.

No spray drying process parameters, guidance or even suggestion of the same are provided in any of the cited references and determination of the same would require undue experimentation.

Applicant understands that a further test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that the

cited references satisfy the enablement requirement and whether the complex and necessary extensive experimentation is "undue."

In *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), the Court indicated that the factors to be considered when determining whether experimentation is undue include but are not limited to:

- (i) The breadth of the claims;
- (ii) The nature of the invention;
- (iii) The state of the prior art;
- (iv) The level of one of ordinary skill;
- (v) The level of predictability in the art;
- (vi) The amount of direction provided in the disclosure;
- (vii) The existence of working examples in the disclosure; and
- (viii) The quantity of experimentation needed to make the compositions based on direction provided in the disclosure.

Evidence that the Miyajima, Kigoshi and Hikosaka References are Non-Enabling to Make the Claimed Spray Dried Dispersions - the Mere Mention of the term "Spray Drying" being Insufficient to Provide the Necessary Guidance and Experimentation Necessary to do the Same Would Be Undue

Based on all of the *Wands* factors (as discussed below), Miyajima, Kigoshi and Hikosaka are not enabling and any experimentation in attempt to make the claimed spray dried compositions would be undue under the law.

- (i) The breadth of the claims – Miyajima, Kigoshi and Hikosaka do not teach or suggest how to make the claimed spray dried dispersions.
- (ii) The nature of the invention – none of Miyajima, Kigoshi and Hikosaka is directed to spray dried dispersions.
- (iii) The state of the prior art – the prior art of record does not teach or suggest how to make the claimed spray dried dispersions; nothing provides even a hint of guidance as to any of the necessary information as set forth above.
- (iv) The level of one of ordinary skill – the level of skill is that of a chemist or chemical engineer or physicist with a Bachelors of Science or higher degree.
- (v) The level of predictability in the art – the level of predictability in the art is low, as the predictability of chemistry in general is low, especially in light of the fact that there is a multitude of parameters, components and other such factors required to produce a suitable spray dried dispersion composition as claimed.
- (vi) The amount of direction provided by the disclosure – there is no direction provided in any of the references cited as how to make the claimed spray dried dispersion compositions or any spray dried composition at all. This issue is discussed above.

(vii) The existence of working examples – there are no examples in the cited references showing or describing how to make the claimed spray dried dispersion compositions.

(viii) The quantity of experimentation needed based on the content of the references – spray dried dispersions require methods having a complex set of parameters, conditions and methodologies. Varying all these different parameters, conditions and methodologies, to make the claimed spray dried dispersion compositions with the desired physical characteristics, considering it from the standpoint of simple mathematics, *per se* illustrates the extensive quantity of experimentation that was required for the inventors to develop the disclosed invention.

Weighing the eight factors above, it is a fair conclusion that the cited references require undue experimentation and, thus, are not enabling for making a spray dried dispersion consisting of a sparingly water-soluble drug and hydroxypropyl methylcellulose acetate succinate (HPMCAS), said drug being molecularly dispersed and amorphous in said dispersion, having a drug:polymer weight ratio between 1:0.4 and 1:20, and said dispersion is a homogeneous solid solution of said drug in said HPMCAS.

#### **Claim Rejections - 35 U.S.C. § 102**

*Claims 1, 4, 23, 49-51, 53-56 and 5-8 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Miyajima et al. (EP 0 344 603).* This rejection is respectfully traversed.

Miyajima fails to teach a spray dried HPMCAS/drug molecularly dispersed and completely amorphous solid dispersion. As shown above, producing a completely amorphous solid dispersion of HPMCAS/drug combination is not inherently disclosed in Miyajima. Further, Miyajima fails to disclose how to spray dry such a solid dispersion and as such, cannot be tested nor considered as prior art for a spray dried HPMCAS/drug molecularly dispersed and completely amorphous solid dispersion.

Applicant respectfully requests withdrawal of the rejection.

*Claims 1, 4, 49-51 and 53-56 are rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Kigoshi et al. (EP 0 784 974).* This rejection is respectfully traversed.

Kigoshi fails to teach a spray dried HPMCAS/drug molecularly dispersed and completely amorphous solid dispersion. As shown above, producing a completely amorphous solid dispersion of HPMCAS/drug combination is not inherently disclosed Kigoshi. Further, Kigoshi fails to disclose how to spray dry such a solid dispersion and as such, cannot be tested nor considered as prior art for a spray dried HPMCAS/drug molecularly dispersed and completely amorphous solid dispersion.

Applicant respectfully requests withdrawal of the rejection.

*Claims 1, 4, 49, 53, 54, 55, 56 and 58 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Hikosaka (JP 57-176907).* This rejection is respectfully traversed.

Hikosaka fails to teach a spray dried HPMCAS/drug molecularly dispersed and completely amorphous solid dispersion. As shown above, producing a completely amorphous solid dispersion of HPMCAS/drug combination is not inherently disclosed in Hikosaka. Further, Hikosaka fails to disclose how to spray dry such a solid dispersion and as such, cannot be tested nor considered as prior art for a spray dried HPMCAS/drug molecularly dispersed and completely amorphous solid dispersion.

Applicant respectfully requests withdrawal of the rejection.

**35 U.S.C. § 103**

*Claims 1, 23, 50 and 51 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Miyajima et al. (EP 0 344 603) or Kigoshi et al. (EP 0 784 974).* This rejection is respectfully traversed.

Because neither reference teaches a spray dried HPMCAS/drug molecularly dispersed and completely amorphous solid dispersion, the combination of the references does not teach or suggest the claimed solid dispersions. As shown above, producing a completely amorphous solid dispersion of HPMCAS/drug combination is not inherently disclosed in either reference. Further, the references fail to disclose how to spray dry such a solid dispersion and as such, cannot be tested nor considered as prior art for a spray dried HPMCAS/drug molecularly dispersed and completely amorphous solid dispersion.

Applicant respectfully requests withdrawal of the rejection.

*Claims 1, 4, 36, 37, 49-51 and 53-56 rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Kigoshi et al. (EP 0 784 974) in view of Madhusoodanan et al. ("Efficacy of risperidone treatment for psychoses associated with schizophrenia, schizoaffective disorder, bipolar disorder, or senile dementia in 11 geriatric patients: a case series," in J. Clin. Psychiatry, 1995 Nov;56(11):514-8) and further in view of Bymaster et al. (6,147,072).* This rejection is respectfully traversed.

Because none of these references teach a spray dried HPMCAS/drug molecularly dispersed and completely amorphous solid dispersion, the combination of the references does not teach or suggest the claimed solid dispersions. As shown above, producing a completely amorphous solid dispersion of HPMCAS/drug combination is not inherently disclosed in the primary reference and the Examiner does not assert that the other references disclose such (as they do not). Further, the references fail to disclose how to spray dry such a solid dispersion and as such, cannot be tested nor considered as prior art for a spray dried HPMCAS/drug molecularly dispersed and completely amorphous solid dispersion.

Applicant respectfully requests withdrawal of the rejection.

Based on the foregoing, Applicants respectfully submit that the claims are directed to allowable subject matter and that the application is in condition for allowance. Should the Examiner believe that anything further is necessary to place this application in better condition for allowance, the Examiner is requested to contact Applicants' representative by telephone.

Respectfully submitted,

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